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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,527	BRANDT ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 6/06/2007. Currently Claims 1, 4-18 are pending. Claims 2-3 have been cancelled.

2. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP §821.01. Specifically, the reply filed 8/10/2006 picked the combination of polymorphic sequences D7S522, D8258, and D16S400; therefore the claims should be amended to remove polymorphic sequences, which were not elected in the requirement for restriction.

3. The following rejections for Claims 1 and 4-18 are necessitated by amendment or reiterated. Response follows.

4. This action is Final.

Withdrawn Objections

5. The objection to the specification made in section 4 of the previous office action is moot based on amendment to the specification.

6. The objection to claim 8 made in section 5 of the previous office action is moot based on the amendments to the claims to incorporate sequence identifiers.

Withdrawn Rejections

7. The rejections of Claims 1-16 under 35 USC 112/2nd paragraph made in section 6 of the previous office action is moot based on amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1 and 4-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detection and characterization of prostate tumors by the isolation of cyokeratin-positive cells by immunomagentic cell isolation comprising analysis of D7S522, D8S258, and D16S400 in a PCR amplification method, does not reasonably provide enablement for the detection of ANY tumor using ANY cell cluster isolated by ANY isolation method comprising analysis of ANY genetic change in ANY amplification method.

It is noted that though the specification is unclear with regard to the correlation of LOH of D7S522, D8S258, and D16S400 with prostate tumors, the art known at the time of filing does indicate a correlation of these three microsatellites with detection of prostate tumor.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 1 is drawn to a method to characterize primary tumors comprising isolating or concentrating cell clusters of tumor cells in a sample and determining the genotype of microsatellite and characterizing the primary tumor or separate areas of the tumor. Claim 4 defines the polymorphic sequences analyzed. Claim 5 is drawn to a method wherein the polymorphic DNA is reproduced before analysis. Claim 6 defines the polymorphic sequences. Claim 7 defines the analysis method. Claim 8 defines the primer pairs used for reproduction. Claim 9 defines the analysis by capillary electrophoresis. Claim 10 is drawn to a method wherein tumor cells cytokeratin-positive cells are isolated from sample material and/or positive epithelial cells. Claim 11 is drawn to concentration epithelial cells by a density gradient centrifugation and removing cytokeratin-positive and/or positive cell clusters from tissue specific proteins by immunomagnetic cell isolation. Claims 12-13 define the hyperosmotic medium. Claim 15 is drawn to the using of the method. Claim 16 defines the detection to specific carcinomas. Claim 17 defines the polymorphic DNA. Claim 18 defines the reproduction by primer pairs.

The claims are broadly drawn to the detection of ANY tumor using ANY cell cluster isolated by ANY isolation method comprising analysis of ANY genetic change in ANY amplification method.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts a method for the characterization of primary tumors and separate areas of primary tumors (abstract). The specification asserts a method of isolating and concentrating clusters of tumors cells extracted from sample material followed by analysis of genetic changes in isolated cell clusters (abstract).

The specification asserts analysis of microsatellites can be used to detect genetic changes (p. 2 paragraphs 12 and 13). The specification asserts characterization, quantification, and prognosis for tumors were achieved by testing alteration in microsatellite DNA (p. 2 paragraph 14). The specification does not teach an association of ANY genetic change with detection of ANY tumor. It is unpredictable that any genetic change can be used to detect any primary tumor. The skilled artisan would have to perform undue experimentation to determine which genetic changes are associated with which tumors.

The specification asserts a method of detection using a multiplex PCR of microsatellites (p. 2 paragraph 16). The specification asserts that the microsatellites

were separated by capillary electrophoresis (p. 2 paragraph 16). The specification does not teach other methods of analyzing genetic changes.

The specification asserts tumor cells to be tested from samples would be isolated or concentrated by adding epithelial cells by density gradient centrifugation, followed by immuno-magnetic isolation or concentration of cytokeratin-positive cell clusters (p. 2-3 paragraph 22). The specification asserts addition of hyper-osmolarity during the density gradient centrifugation causes the cells in the cell clusters to shrink so that the columns are not blocked by cell clusters leading to a increased yield of tumor cells from the sample (p. 3 paragraph 24). It is unclear if any isolation method would be able to increase the yield of tumor cells in the sample material to a concentration wherein microsatellite LOH could be tested.

The claims are further drawn to application of the method for the detection or characterization of tumors from various cancers to determine the clonality from the cell clusters, the tumor stage, the metastasizing potential, therapy requirements, efficacy of therapy, and assessment of the course of a disease or therapy. The specification has not described any of these uses or provided any examples of these uses. It is unpredictable to use a correlation of a genetic alteration with a particular tumor to determine the tumor stage, metastasizing potential, therapy requirements, efficacy of therapy, and assessment of the course of the disease or therapy. The skilled artisan would have to perform numerous undue experimentations in order to use the method of detection in any of the preceding uses.

Working Examples

The specification asserts a method of isolating DNA from cytokeratine-positive tumor cells (p. 7 paragraph 205). The specification asserts a method of isolating DNA from preserved tumor tissue (p. 7 paragraph 207). The specification asserts a method of isolating DNA from full blood (p. 7 paragraph 208).

The specification asserts three multiplex PCRs were performed including the combination of D7S522, D8S258, and D16S400 (p. 8 paragraph 214).

Table 5 shows comparison of genetic alterations between two foci and circulating blood in three patients (p. 10-11). The specification asserts that the two foci are separate foci of the primary tumor gained from the DNA of peripheral blood (p. 10 paragraph 230). The specification asserts that the samples for the patients were prostate tissue samples (p. 10 paragraph 230). The specification has not clearly defined what the two foci encompass. It is clear from the specification that prostate tumors are tested, however, it is unclear what foci 1 and 2 represent. It is not clear if the two foci represent different regions of the tumor and if so which region is deemed foci 1 and which region is deemed foci 2.

The specification asserts testing 6 patients (Table 5 pgs. 10-11). The patients were tested for the microsatellite D7S522 in circulating cells and in two foci. With regard to patients 1 and 5, it seems that if the circulating cells are tested and there is LOH then the patient has foci 1 tumor (Table 5 pgs. 10-11). However, the same correlation cannot be made in patient 2, 3, 4 and 6. Further it is not clear from the table if homozygotes are the same as no loss of heterozygosity. Therefore it is unclear if

there is any correlation of detection of microsatellite D7S522 with detection and characterization of tumor cells.

With regard to microsatellite D16S400, in patients 2 and 5, it seems that if the circulating cells are tested and there is LOH then the patient has focus 1 tumor (Table 5 pgs. 10-11). However, the same correlation cannot be made in patient 1, 3, 4 and 6. Therefore it is unclear if there is any correlation of detection of microsatellite D16S400 with detection and characterization of tumor cells.

With regard to microsatellite D8S258, in patient 1, it seems that if the circulating cells are tested and there is LOH in allele 1 then the patient has focus 1 tumor (Table 5 pgs. 10-11). With regard to patients 3 and 6, the circulating cells tested no loss of heterozygosity. Focus 1 had LOH and focus 2 had no LOH. However, it is unpredictable to make a correlation that if a patient has no loss of heterozygosity then they have focus 2 tumor. There is no correlative data, which shows that any patient with no LOH will have focus 2 tumor. With regard to patient 4, there seems to be data that there is LOH in the circulating cells and both focus tumors. However, the specification has not shown if this microsatellite shows LOH in any sample regardless of rather the patient has a tumor. Therefore it is unclear if there is any correlation of detection of microsatellite D16S400 with detection and characterization of tumor cells.

The specification asserts that by analyzing microsatellite DNA, circulating cells can be directly assigned to certain foci of primary tumors. However, the specification does not clearly show a correlation of the results of microsatellite DNA in circulating cells being definitive to a specific foci.

The unpredictability of the art and the state of the prior art

Ichikawa et al. (International Journal of Clinical Oncology 2000 Vo. 5 p. 345) teaches that there is a great deal of variability between studies of allelic losses on chromosome arms and prostate cancer (Abstract). Ichikawa et al. teaches that there are discrepancies in the genetic findings depending on the methods of detection employed (abstract). Ichikawa et al. teaches that molecular genetic studies using PCR analysis of microsatellite markers demonstrated allelic loss in a region whereas fluorescence in situ hybridization analysis showed a gain at the same region (Abstract). Therefore, the art teaches that based on the type of analysis method different results can occur. The art teaches the results of the detection and characterization of tumors changes dependent on the analysis method.

Uchida et al. (Oncogene 1995 Vol. 10 p. 1019) teaches that genetic alterations can be observed in high grade and advanced prostate cancers but are rare in low grade or early prostate cancers. The art teaches that genetic alterations can be used to characterize tumors but this characterization is dependent on the type of cancer or how long the patient has had the cancer. Therefore, it is unclear it any genetic alteration can be used to detect and characterize any tumor.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters that would have to be studied. To practice the invention as broadly as it is claimed, the skilled artisan would be required to first determine the correlation of any genetic change with detection of any tumor. The skilled artisan would have to determine if any isolation method would concentrate cell clusters in a large enough concentration to test genetic alterations. The skilled artisan would

have to determine which analysis methods provided the same correlative results. The skilled artisan would finally have to take the correlative results and use them in methods of determining the stage of the tumor and metastasizing potential. The skilled artisan would have to take the correlative results and determine if the genetic change effect therapy of a patient.

The art teaches that the correlation of genetic changes and detection of tumors is affected both by the type and age of the tumor and by the analysis method used to test the genetic change. The current state of the art does not support a predictable prediction of the detection of ANY tumor with ANY genetic change.

To use the invention as presented would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the scope of the claims because the scope of the claims include detection of ANY tumor with ANY genetic alteration using ANY cell cluster isolation method and ANY genetic analysis method. Without sufficient guidance, determination of the correlation of genetic change and tumor is unpredictable and the experimentation left to those skilled in the art is extensive. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to,

and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The reply traverses the rejection. The reply asserts that the art shows that cell clusters can be isolated from a liquid sample by many means and therefore can isolate the clusters from body fluids (p. 10 3rd paragraph). The reply asserts that the formation and spread of malignant tumors and accumulation of multiple genetic changes is well known and can be identified using microsatellite markers (p. 10 last paragraph). The reply points to Ankar et al. which discloses the use of microsatellite markers for characterization of primary tumors (p. 10 last paragraph and p. 11 1st paragraph). The reply asserts that one of ordinary skill in the art would recognize that polymorphic DNA at microsatellite markers can be used to determine tumor development, metastasizing potential, therapy requirements, efficacy of therapy, and assessment of the course of a disease or therapy (p. 11 1st paragraph).

Though the art is clear that cell clusters can be isolated from fluid, it is still unpredictable that any cell cluster can characterize primary tumors or separate areas of the primary tumors by the use of any microsatellite marker. The working example in the specification shows unpredictability with the correlation of microsatellites and two foci of a tumor. As discussed above, D7S522 was correlated in two patients with foci 1 tumor but not with 4 other patients (Working examples). The specification shows

unpredictability with the association of microsatellite DNA and certain foci of primary tumors because the results seem to indicate that there is correlation in some patients and not in other patients.

Further the ~~are~~ art shows that there is variability in genetic alteration in advanced cancer and low grade cancer. Uchida et al. teaches that genetic alterations observed in advanced prostate cancers are not seen in low grade prostate cancers, therefore the art indicates that microsatellite detection is not correlative with any type of cancer.

The response point to Ankar et al. as support for the detection of tumors using clinical samples. However, Ankar et al. teaches the use of microsatellite instability in the plasma as tumor markers greatly depends on the kind of cancer studied (p. 69 2nd column 1st full paragraph). Ankar et al. envisages a future wherein detection test for some malignancies whereas for others only prognosis test or a follow-up test seems possible (p. 69 2nd column 1st full paragraph).

Therefore, the art and the specification show the unpredictability of characterizing tumors or separate areas of primary tumors using microsatellite detection. As shown in the argument above, it is unpredictable to correlate any tumor or separate areas of tumors with detection of microsatellite markers because the art and the specification teach that these correlations are unpredictable.

The claims are further drawn to the method of characterization, which further comprises determining the tumor development, metastasizing potential, therapy requirements, efficacy of therapy, and assessment of the course of a disease or therapy. The specification has not described any of these uses or provided any

examples of these uses. It is unpredictable to use a correlation of a genetic alteration with a particular tumor to determine the tumor stage, metastasizing potential, therapy requirements, efficacy of therapy, and assessment of the course of the disease or therapy. The skilled artisan would have to perform numerous undue experimentations in order to use the method of detection in any of the preceding uses. The skilled artisan would have to perform undue experimentation, for example, to determine which therapy requirements would be correlative to particular microsatellite markers. This would require many experimental steps without an expectation of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 5, and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Sidransky et al. (WO 96/06951 March 7, 1996).

With regard to Claim 1, Sidransky et al. teaches a method of an assay for the detection of microsatellite loci (genetic changes) to detect primary tumors within a patient (abstract).

With regard to Claim 1i, Sidransky et al. teaches detecting a clonal populations of cells in the DNA of samples including urine (p. 6 lines 8-10). Sidransky et al. teaches

using the urine sediment (e.g. urine which has been spun in a centrifuge) of a group of patients (p. 39 lines 13-15). Urine sediment is concentrates all cells in the urine and therefore, concentrates tumor cells. Sidransky et al. teaches that this clinical sample has clonal population of cells (e.g. cell clusters) that are detectable by microsatellite alterations (p. 6 lines 8-10).

With regard to Claim 1ii, Sidransky et al. teaches a method comprising isolating the nucleic acid present in the sample and detecting the presence or the absence (loss of heterozygosisity, LOH) of the hypermutable target nucleic acid, following amplification of the nucleic acid (p. 6, lines 13-16).

With regard to Claim 1iii, Sidransky et al. teaches characterizing the primary tumor (e.g. detecting) (abstract).

With regard to Claim 5, Sidransky et al. teaches a method using PCR to detect the microsatellite markers (p. 36 lines 27-28). The PCR method is a polymerase chain reaction, which would reproduce the polymorphic DNA to increase the fragment concentration. Sidransky et al. teaches detecting microsatellite alterations (polymorphic DNA) in both tumors and urine sample (cell clusters) (p. 36 liens 1-5 and 19-23 and Figure 4). These findings are recorded on a gel image (e.g. analysis) (Figure 4).

With regard to Claim 15, Sidransky et al. teaches a method of detection of metastatic sites within a patient (metastasizing potential) (abstract).

With regard to Claim 16, Sidransky et al. teaches detection of breast cancers, prostate, and bladder cancers (p. 11 lines 24-30).

Response to Arguments

The reply traverses the argument. The reply asserts that Sidransky et al. does not teach isolating clusters of tumors from body fluids to characterize solid tumors.

The argument has been fully considered but has not been found persuasive.

As the rejection discloses above, Sidransky et al. teaches detecting (characterizing) solid tumors by detecting microsatellite markers in fluid samples such as urine. Sidransky et al. teaches concentrating the cells present in urine before amplification by centrifuging (e.g. urine sedimentation). Sindransky et al. teaches the cells present in a sample are detected as a clonal population of cells (e.g. cell cluster) (p. 6 lines 7-10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 4, 6-7, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sidransky et al. (WO 96/06951 March 7, 1996) in view of Jenkins et al. (Genes, Chromosomes and Cancer 1998 Vol. 21 p. 131) and Osman et al. (Intl. J. Cancer 1997 Vo. 71 p. 580).

Sidransky et al. teaches a method of an assay for the detection of microsatellite loci (genetic changes) to detect primary tumors within a patient (abstract). Sidransky et al. teaches a method comprising isolating the nucleic acid present in the sample and detecting the presence or the absence (LOH) of the hypermutable target nucleic acid, following amplification of the nucleic acid (p. 6, lines 13-16).

With regard to Claim 7, Sidransky et al. teaches a method using PCR to detect the microsatellite markers (p. 36 lines 27-28).

However, Sidransky et al. does not teach a method of detection using D7S522, D8S258, and D16S400.

With regard to Claim 4 and 17, Jenkins et al. teaches detection of D7S522 and D8S258 to detect tumor progress in prostate cancer (abstract).

With regard to Claim 6, Jenkins et al. teaches the analysis of both markers together (Table 1 p. 133 and Figure 1 p. 135).

With regard to Claim 4 and 17, Osman et al. teaches the molecular genetic analysis of prostate cancer using D16S400 (abstract and p. 580 2nd column last paragraph).

With regard to Claim 6, teaches the analysis of the marker (Table 1 p. 581 and Figure 1 p. 581).

Therefore it would have be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Sidransky et al. to analyze all microsatellites associated with a particular tumor type. The ordinary artisan would be motivated to analyze microsatellite markers of Jenkins et al. and Osman et al. because both teach that these markers can detect prostate cancer. The ordinary artisan would be motivated to analyze the microsatellites of Jenkins et al. because Jenkins et al. teaches these microsatellites are strongly associated with systemic progression and prostate cancer death (abstract). Further the ordinary artisan would be motivated to analyze the microsatellites of Osman et al. because Osman et al. teaches alterations on the long arm of chromosome 16 are frequent events in prostate cancer (abstract). The ordinary artisan would be motivated to analyze both sets of microsatellite markers in order to have a full analysis of genetic alterations in order to describe the tumor.

Response to Arguments

The reply traverses the argument. The reply asserts that Sidransky et al. does not teach isolating clusters of tumors from body fluids to characterize solid tumors.

The argument has been fully considered but has not been found persuasive.

As presented in the response to arguments in the 35 USC 102(b) rejection above, Sidransky et al. teaches concentration of urine sample and therefore the concentration of tumor cells contained in the sample. Sindransky et al. teaches the cells present in a sample are detected as a clonal population of cells (e.g. cell cluster) (p. 6 lines 7-10).

12. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sidransky et al. (WO 96/06951 March 7, 1996) in view of Zhang et al. (Nucleic Acids Research 1999 Vol. 27 e36).

Sidransky et al. teaches a method of an assay for the detection of microsatellite loci (genetic changes) to detect primary tumors within a patient (abstract). Sidransky et al. teaches a method comprising isolating the nucleic acid present in the sample and detecting the presence or the absence (loss of heterozygosity, LOH) of the hypermutable target nucleic acid, following amplification of the nucleic acid (p. 6, lines 13-16).

However, Sidransky et al. does not teach a method using capillary electrophoresis.

With regard to Claim 9, Zhang et al. teaches a method of separation using capillary electrophoresis (abstract). Zhang et al. teaches a method of detecting microsatellite markers using capillary electrophoresis (p. V 2nd column last paragraph).

Therefore it would have be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Sidransky et al. to analyze the microsatellites with capillary electrophoresis. The ordinary artisan would be motivated to analyze microsatellite markers with capillary electrophoresis as taught by Zhang et al., because Zhang et al. teaches capillary electrophoresis provides low-cost, easily automated and rapid DNA sequencing (p. I 1st paragraph). The ordinary artisan would be motivated to use capillary electrophoresis with microsatellite markers because Zhang et al. teaches the patterns are clearly resolved and identification of pattern is easy (p. V last sentence). Zhang et al. teaches DNA fragment sizes can be accurately determined and directly compared (p. VI 1st paragraph).

Response to Arguments

The reply traverses the argument. The reply asserts that Sidransky et al. does not teach isolating clusters of tumors from body fluids to characterize solid tumors.

The argument has been fully considered but has not been found persuasive.

As presented in the response to arguments in the 35 USC 102(b) rejection above, Sidransky et al. teaches concentration of urine sample and therefore the concentration of tumor cells contained in the sample. Sindransky et al. teaches the cells

present in a sample are detected as a clonal population of cells (e.g. cell cluster) (p. 6 lines 7-10).

13. Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sidransky et al. (WO 96/06951 March 7, 1996) in view of Brandt et al. (Clinical Chemistry 1996 Vol 42 p. 1881).

Sidransky et al. teaches a method of an assay for the detection of microsatellite loci (genetic changes) to detect primary tumors within a patient (abstract). Sidransky et al. teaches a method comprising isolating the nucleic acid present in the sample and detecting the presence or the absence (loss of heterozygosity, LOH) of the hypermutable target nucleic acid, following amplification of the nucleic acid (p. 6, lines 13-16).

However, Sidransky et al. does not teach a method of isolation from positive epithelial cells.

With regard to Claim 10, Brandt et al. teaches a two-layer buoyant density centrifugation gradient for enrichment of prostate derived cells and cell clusters from blood (title). With regard to Claim 11, Brandt et al. teaches a method of combined buoyant density gradient immunomagenetic separation which enriches prostate derived cells from peripheral blood (p. 1881 2nd column 1st paragraph).

With regard to Claim 12-13, Brandt et al. teaches the use of PolymorphPrep and NycoPrep (p. 1881 2nd column 2nd paragraph).

Therefore it would have be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Sidransky et al. to perform isolation as taught by Brandt et al. The ordinary artisan would be motivated isolate cells as taught by Brandt et al., because Brandt et al. teaches in order to have satisfactory clinical management of prostate cancer requires sensitive markers for the detection of metastasis (p. 1881 1st column last paragraph and 2nd column 1st paragraph). Brandt et al. teaches a method to enrich prostate derived cells from peripheral blood to use in detection (p. 1881 2nd column 1st paragraph). The ordinary artisan would be motivated to use the isolation method of Brandt et al. because Brandt et al. teaches that is easer and quicker to perform and has a high recover of prostate-derived cells (p. 1881 last sentence).

Response to Arguments

The reply traverses the rejection. The reply asserts that Brandt et al. discloses the preparation of cancer cell clusters by density gradient separation, but does not disclose primary tumors or separate areas of primary tumors can be characterized by microsatellite markers (p. 12 last paragraph). The reply asserts Sidranksy et al. does not teach or suggest using clusters of cells in the assay of microsatellite loci (p. 12 last paragraph).

These arguments have been thoroughly considered but have not been found persuasive.

Sidransky et al. teaches concentration of urine sample and therefore the concentration of tumor cells contained in the sample. Sindransky et al. teaches the cells present in a sample are detected as a clonal population of cells (e.g. cell cluster) (p. 6 lines 7-10). Therefore, Sidransky et al. teaches detecting cell clusters using microsatellites. Brandt et al. teaches a method of enriching the cell clusters in clinical samples. The ordinary artisan would be motivated to enrich the clinical samples of Sidransky et al. in order to increase the concentration of cell clusters and therefore increase the sensitivity of the microsatellite assay.

14. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sidransky et al. (WO 96/06951 March 7, 1996) in view of Girard et al. (Cancer Research 2000 Vol 60 p. 4894).

Sidransky et al. teaches a method of an assay for the detection of microsatellite loci (genetic changes) to detect primary tumors within a patient (abstract). Sidransky et al. teaches a method comprising isolating the nucleic acid present in the sample and detecting the presence or the absence (loss of heterozygosity, LOH) of the hypermutable target nucleic acid, following amplification of the nucleic acid (p. 6, lines 13-16).

However, Sidransky et al. does not teach analysis by cluster analysis.

With regard to Claim 14, Girard et al. teaches a method of clustering analysis to determine correlations between LOH on different chromosomes (Abstract). Girard et al. teaches a method of cluster analysis for microsatellite markers (p. 4896 2nd column Cluster analysis).

Therefore it would have be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Sidransky et al. to perform cluster analysis on the detected microsatellite markers as taught by Girard et al. The ordinary artisan would be motivated to analysis detected microsatellite markers by cluster analysis as taught by Girard et al., because Girard et al. teaches that clustering analysis uncovers previous unknown iterations between sites of allelic loss (p. 4894 2nd column near end of last paragraph). The ordinary artisan would be motivated to perform clustering analysis to determine correlations between LOH on different chromosomes (Abstract).

Response to Arguments

The reply traverses the argument. The reply asserts that Sidransky et al. does not teach isolating clusters of tumors from body fluids to characterize solid tumors.

The argument has been fully considered but has not been found persuasive.

As presented in the response to arguments in the 35 USC 102(b) rejection above, Sidransky et al. teaches concentration of urine sample and therefore the concentration of tumor cells contained in the sample. Sindransky et al. teaches the cells

present in a sample are detected as a clonal population of cells (e.g. cell cluster) (p. 6 lines 7-10).

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

JEANINE A. GOLDBERG
PRIMARY EXAMINER
8/8/07